

Q25
ord.

	(SEQ ID NO:111)		
4	GTAGGCCCGGTGCAGCGT GTCATACAGATGG (SEQ ID NO:112)	31-mer	oligonucleotide specific for HC2B, 2C, 2D and 2E based upon specific exon sequence found at nucleotide 3153. Can eliminate function of these CLASP-2 isoforms.
5	GCAATGTCTGAGACTTTC GATCATGAACTATG (SEQ ID NO:113)	32-mer	oligonucleotide specific for HC2A, 2B, 2E, and 2F. Encompasses nucleotides 1987-2018. Can eliminate function of these CLASP-2 isoforms.
6	CAGGAGCTGGTTCTTAAA (SEQ ID NO:114)	18-mer	oligonucleotide specific for HC2A, 2D and 2E. Encompasses nucleotides 2213-2230. Can eliminate function of these CLASP-2 isoforms

Table 5 legend. All nucleotide numeration are relative to Human CLASP-2A (HC2A). See FIG. 2B.

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 175, at the end of the application.

REMARKS

Applicants request entry of this amendment in adherence with 37 C.F.R. §§ 1.821-1.825. This amendment is accompanied by a floppy disc containing the above named sequences, SEQ ID NOS:1-152, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disc.


The information contained in the computer readable disc was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter. Attached hereto is a marked up version of the changed made to the specification by the current amendment. The attached pages are entitled "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Peter S. Lu
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PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,


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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning on page 3, line 21, has been amended as follows:

In another aspect, the invention provides a CLASP-2 polynucleotide that encodes a polypeptide having the full-length sequence of Isoform 1, Isoform 2, or Isoform 3 (SEQ ID NO:[] 1, 3, and 5) or the cDNA sequence encoded by the inserts of AVC-PD14 (ATCC Deposit No. [] PTA-2611) and AVC-PD19 (ATCC Deposit No. [] PTA-2614).

The paragraph beginning on page 6, line 11, has been amended as follows:

Figure 1. Nucleotide and predicted amino acid sequence of CLASP-2A cDNA (SEQ ID NOS:1 and 2). Notable protein motifs are indicated above the nucleotide sequence in bold. Potential initiator methionines are underscored. The notable, predicted protein motifs are: a cadherin cleavage site encoded by nucleotides 854-868, a cadherin ectodomain (EC) encoded by nucleotides 1253-1264, a transmembrane domain encoded by nucleotides 2861-2917, a coiled coil domain encoded by nucleotides 3579-3682, a second coiled coil domain encoded by nucleotides 3827-3937, and a PDZ binding motif (PBM) encoded by nucleotides 4046-4057.

The paragraph beginning on page 6, line 18, has been amended as follows:

Figure 2. A. Schematic of CLASP-2 splice variants. Splice variants are compared to Human (h) CLASP-2A. Numbers above hCLASP-2A line diagram indicate where splice variations comprising deletions and insertions relative to hCLASP-2A are found. Abbreviations: "KIAA" KIAA1058 sequence (Genbank Accession No. AB028981). **B.** Nucleotide and predicted amino acid sequence of CLASP-2A cDNA (SEQ ID NOS:1 and 2). Notable protein motifs are indicated above the nucleotide sequence in bold. Exact position of insertions and deletions are indicated above the CLASP-2A sequence with arrows and "x", respectively. The nucleotide sequence of insertions schematized in FIG. 2A are indicated above the arrow. The insertions and deletions are as follows (numeration refers to Human CLASP-2A nucleotide sequence): Nucleotides 1966-2034 are deleted in CLASP-2D.

Nucleotides 2219-2224 are deleted in CLASP-2B. There is an insertion of 69 [amino acids] nucleotides at nucleotide 2927 found in CLASP-2D. The nucleotide sequence for this insertion is:

AAGCAGTCCAGTGGGAGCCGCCCCTTCTCCCCACAGCCATAGCGCCTGCCTGAG
GAGGAGCCGGGGAG (SEQ ID NO:11) and encodes amino acids

AVQWEPPLPHSHSACLRRSRG (SEQ ID NO:12) (one letter amino acid abbreviation).

This amino acid sequence encodes a putative SH3 binding domain. There is another deletion at between nucleotides 3011-3079 found in CLASP-2E. CLASPs 2B, 2C, 2D and 2E contain an insertion at nucleotide 3153 with the nucleotide sequence

of: TGAGAGGCTGGCCCATCTGTATGACACGCTGCACCGGGCCTACAGCAAAGTGA
CCGAGGTCATGCACTCGGGCCGCAGGCTTCTGGGGACCTACTTCCGGGTAGCCTT
CTTCGGGCAGGCAGCGCAATACCAGTTTACAGACAGTGAAACAGATGTGGAGGG
ATT (SEQ ID NO:13). The entire sequence is found in CLASP-2D and encodes amino acids

ERLAHLYDTLHRAYSKVTEVMHSGRLLGTYFRVAFFGQAAQYQFTDSETDVEG
(SEQ ID NO:14) while the underline sequence is found in CLASPs 2B, 2C, and 2E and encodes amino acids ERLAHL YDTLHRAYSKVTEVMHSGRLLGTYFRVAFFGQG

(SEQ ID NO:15). This amino acid sequence encodes a putative immunoreceptor tyrosine-based activation motif (ITAM). There is a two nucleotide deletion in Human CLASP-2C found at nucleotides 3586 and 3587. There is an insertion of 8 nucleotides found only in Human CLASP-2D with sequence: CTGGGATG at nucleotide 3937. This insertion puts a stop codon into the CLASP-2D nucleotide sequence.

The paragraph beginning on page 7, line 16, has been amended as follows:

Figure 3. A. Alignment of nucleotide sequences of the CLASP-2 isoforms (SEQ ID NOS:1, 3 5, 7, 9, 16, and 18). Sequences were aligned using ClustalW **B.** Alignment of amino acid sequence of the CLASP-2 isoforms(SEQ ID NOS:2, 4, 6, 8, 10, 17, and 19). Sequences were aligned using ClustalW. One letter amino acid abbreviation is used.

The paragraph beginning on page 8, line 3, has been amended as follows:

Figure 5. A. Amino acid sequence of human and rat CLASP proteins.

Sequences were aligned using ClustalW. One letter amino acid abbreviation used. Protein motifs are found within the labeled boxes. A “-” indicates gaps that are placed to acquire a best overall alignment. Other abbreviations: “HC2A” Human CLASP-2 sequence (SEQ ID NO:2), “KIAA” KIAA1058 sequence (SEQ ID NO:7) (Genbank Accession No. AB028981), “rat” TRG gene (SEQ ID NO:20) (Genbank Accession No. X68101), “HC4” Human CLASP-4 sequence (SEQ ID NO:21), “HC1” Human CLASP-1 sequence (SEQ ID NO:22), “HC3” Human CLASP-3 sequence (SEQ ID NO:23), “HC5” Human CLASP-5 sequence (SEQ ID NO:24). **B.** Alignment of DOCK motifs found within the human CLASPs and compared to canonical DOCK motifs. Consensus amino acids found within all DOCK motifs are also indicated. Motifs A and B = SEQ ID NOS:25-34; motif C = SEQ ID NOS:35-43; motifs D and E = SEQ ID NOS:44-55; motifs F and G = SEQ ID NOS:56-67.

The paragraph beginning on page 8, line 12, has been amended as follows:

Figure 6. A. Nucleotide (SEQ ID NO:1) and predicted amino acid (SEQ ID NO:2) sequence of CLASP-2A cDNA. Notable protein motifs are indicated (see FIG. 1 legend for details). Additionally, boundaries between exons and introns are indicated by arrows. These boundaries were defined by sequencing Bacterial Artificial Chromosomes (BACs) containing genomic DNA corresponding to CLASP-2 (SEQ ID NOS:68-85). BACs were sequenced using primers derived from exon sequences corresponding to the CLASP-2 cDNA. Each exon/intron boundary is noted (as “Ref” with an appropriate reference number) above the cDNA sequence. The references contain exact nucleotide location of introns. The names and nucleotide numbers of the primers that were used in sequence reactions are also indicated. All nucleotide numbers refer to CLASP-2A cDNA sequence. As shown in the reference, not all of the sequence from sequencing reactions produced sequence matching the cDNA. These nucleotide sequences that did not match the exon sequence for CLASP-2 were considered to be intron sequences. **B.** Alignment of human (SEQ ID NOS:2, 8, and 21-24) and rat (SEQ ID NO:20) CLASP amino acid sequences by ClustalW. Notable protein motifs are indicated (see FIG. 1 Legend for additional details). Additionally, the exon/intron borders described in part A are indicated with vertical lines between appropriate amino acids.

Reference numbers are indicated in the right margin and correspond to references in Fig 6A and B.

The paragraph beginning on page 9, line 17, has been amended as follows:

Figure 9. A. Binding of CLASP-2 C-terminal 20 amino acids to PDZ domains. 20 μ M biotinylated synthetic peptide corresponding to the C-terminal 20 amino acids of CLASP-2 was reacted with the indicated plate bound GST fusion proteins (none = no GST fusion protein coated onto plate). Error bars indicate standard deviation of duplicate measurements. **B.** Affinity of CLASP 2 – PDZ interactions. Varying concentrations of biotinylated CLASP-2 peptide were reacted with plate bound GST alone, GST-DLG1, GST-NeDLG, and GST-PSD95 fusion proteins. The binding to GST alone (< 0.1 OD units) was subtracted from the binding to the fusion proteins and the remaining signal was divided by the signal observed upon addition of 30 μ M CLASP-2 peptide to each PDZ domain-containing protein (0.4 – 1.0 OD units) and plotted. The plotted data was fit to a saturation binding curve, yielding an apparent affinity of 7.5 μ M for NeDLG- CLASP-2 interaction, 21 μ M for DLG1- CLASP-2 interaction, and 45 μ M for PSD95-CLASP-2 interaction. Data are means of duplicate data points, with standard errors between duplicate data points $< 10\%$. **C.** Inhibition of CLASP-2 – PDZ binding. 5 μ M biotinylated synthetic peptide corresponding to the C-terminal 20 amino acids of CLASP-2 was reacted with the indicated, plate-bound PDZ domain-containing GST fusion proteins in the presence or absence of 100 μ M competitor peptide. CLASP-2 Inhibitor refers to a synthetic peptide composed of the eight C-terminal amino acids of CLASP-2. KV1.3 Inhibitor refers to a synthetic peptide composed of the 19 C-terminal amino acids of KV1.3, a lymphocyte potassium channel. The amino acid sequence of the KV1.3 inhibitor is TTNNNPNSAVNIKKIFTDV (SEQ ID NO:86). **D.** Inhibition of KV1.3 – PDZ binding. 5 μ M biotinylated synthetic peptide corresponding to the C-terminal 19 amino acids of KV1.3 was reacted with the indicated, plate-bound PDZ-domain containing GST fusion proteins in the presence or absence of 100 μ M CLASP-2 Inhibitor (see FIG. 9C legend).

The paragraph beginning on page 10, line 9, has been amended as follows:

Figure 10. Preliminary nucleotide (SEQ ID NO:87) and predicted amino acid (SEQ ID NO:88) sequences of CLASP-2 cDNA[s].

The paragraph beginning on page 10, line 10, has been amended as follows:

Figure 11. A) Full length cDNA sequence (SEQ ID NO:118) and predicted amino acid translation (SEQ ID NO:119) of the human CLASP-2 gene. Predicted initiator methionine starts at nucleotide +1. Three independent 1st exons (indicated as 1[1]A (SEQ ID NO:115), 1[1]B (SEQ ID NO:116), and 1[1]C (SEQ ID NO:117)) splice into the second exon starting at nucleotide -101. The sequence appearing in FIG. 1 corresponds to nucleotides 1884 through 6690 of FIG 11A. B) Differences between the human CLASP-2 cDNA isoforms. In addition to the differential first exon usage indicated in A, sequencing multiple, independent cDNA products revealed nucleotide polymorphisms (allelic variations) between CLASP-2 cDNA isoforms. Additionally, differential exon usage through alternative splicing events was discovered. The use of the exon in B leads to a premature stop codon that can generate a soluble form of CLASP-2. C. Schematic of human CLASP-2 cDNAs. The top line represents nucleotide numbering found in FIG. 11A. Line (i) represents CLASP-2 cDNA shown in FIG. 1 above; line (ii) represents the full length CLASP-2 isoforms, where there are three CLASP-2 full length cDNA isoforms (A + Z, B + Z, and C + Z). Each of the isoforms uses a unique first exon (A, B, and C) (*see* FIG. 11A) that splices into the rest of the cDNA from exon 2 onwards represented by Z. The portion of the cDNA represented by Z itself has alternative splice and nucleotide polymorphisms that are shown in FIG. 2 above. Line (iii) represents the additional 5' sequence with a small region of [overlao] overlap between nucleotides 1884 to 2109 in FIG. 11A and nucleotides 1-225 of FIG. 1.

The paragraph beginning on page 10, line 28, has been amended as follows:

Figure 12. Sequence of human CLASP-2 exons and intron boundaries. A Sequence of human CLASP-2 exons and intron borders (SEQ ID NOS:120-133). Stretches of [noncontiguous] noncontiguous genomic sequence from the Human Genome Project (GENBANK entry gi9988160) were aligned using the human CLASP-2 cDNA as a template and Sequencher sequence analysis software (Gene Codes Corp). 22 exons representing

approximately the 5' 20% of the human CLASP-2 cDNA sequence are presented in predicted 5' to 3' order. Exon sequences are underlined and are flanked by intron sequence. Nucleotide numbers in parentheses refer to the exon sequence within the uniquely-generated, contiguous gi9988160 sequence, which is located in **B**. **B**. Ordered stretch of human genomic DNA at the CLASP-2 locus aligned from noncontiguous, shotgun sequencing from the Human Genome Project using the human CLASP-2 sequence from FIG. 5A to determine genomic DNA fragment order and orientation.

The paragraph beginning on page 11, line 8, has been amended as follows:

Figure 13. Amino acid alignment and comparison between the human (h) CLASP family members (SEQ ID NOS:135, 136, 137, 119, 138 and 139). Amino acid sequences were aligned using ClustalW. The alignment is presented in order of their greatest pairwise similarity scores. Single letter amino acid abbreviations are used. [Astericks] Asterisks indicate complete identity, while colons and periods indicate sequence similarity among CLASP family members. Dashes indicate gaps inserted in the amino acid sequence to facilitate alignment. [Labelled] Labeled boxes are domains with similarity to known protein motifs; unlabelled boxes represent regions of similarity between all CLASPs and may represent CLASP-specific domains.

The paragraph beginning on page 22, line 11, has been amended as follows:

The CLASP-2 protein is type I transmembrane glycoprotein, characterized by multiple forms produced by alternative exon usage (*i.e.*, production of splice variants). In one naturally occurring form, CLASP-2 has the structure shown in FIG. 1. However, as discussed in detail *infra*, the CLASP-2 gene encodes a variety of gene product due to alternative splicing of mRNA. FIG. 2 shows the nucleotide sequence and conceptual translation of human CLASP-2 polypeptides. FIGS. 3A and 3B show alignment of the CLASP-2A through 2E nucleotide and amino acid sequences, respectively:

hCLASP-2A cDNA (SEQ ID NO:1) and hCLASP-2A polypeptide (SEQ ID NO:2).

hCLASP-2B cDNA (SEQ ID NO:3) and hCLASP-2B polypeptide (SEQ ID NO:4).

hCLASP-2C cDNA (SEQ ID NO:5) and hCLASP-2C polypeptide (SEQ ID NO:6).

hCLASP-2D cDNA (SEQ ID NO:7) and hCLASP-2D polypeptide (SEQ ID NO:8).

hCLASP-2E cDNA (SEQ ID NO:9) and hCLASP-2E polypeptide (SEQ ID NO:10).

The paragraph beginning on page 24, line 10, has been amended as follows:

The CLASP-2 extracellular domain is characterized by one cadherin EC-like motif (Pigott, R. and Power, C., 1993, The Adhesion Molecule Factbook. Academic Press, pg. 6; Jackson, R. M. and Russell, R. B., 2000, J. Mol. Biol. 296: 325-34). Several highly conserved cysteines are found in the extracellular domain, as well as various glycosylation signals. Through its extracellular domains, CLASP-2 may interact with ligands in a homotypic and/or heterotypic manner to establish the immunological synapse in conjunction with molecules such as TCR, MHC class I, MHC class II, CD3 complex and accessory molecules such as CD4, CD3, ICAM-1, LFA-1, and others. Many cadherins contain a pro-domain of approximately 50 to 150 amino acids that is removed before localization to the plasma membrane. This cleavage is presumed to be carried out by Furin (Posthaus, H. *et al.*, 1998, FEBS Let 438: 306-10) at a consensus sequence of RKQR (SEQ ID NO:89). Furin is a protease that is at least partially responsible for the maturation of certain cadherins. CLASP-2 has the sequence RNQR (SEQ ID NO:90) at nucleotides 945 through 957. By homology, this region is around 120 amino acids into the predicted protein start site for hCLASP-2A. This region may be a pro-domain and cleavage may be required for CLASP-2 function, or aspects of CLASP-2 function.

The paragraph beginning on page 27, line 7, has been amended as follows:

CLASP-2 polypeptides contain a new "DOCK" motif, not previously described in the scientific literature. The CLASP DOCK motif includes a series of five tyrosines surrounded by conserved sequences in regions A, B, C, D, and G (see FIG. 5B). There are also two highly conserved non-tyrosine containing regions [(E and G) separated by nine amino acids] E (P+EXAI+XM; SEQ ID NO:91) and G (LXMXL+GXVXXXVNXG; SEQ ID NO:92) (where X is any amino acid) separated by 20 amino acids.

The paragraph beginning on page 38, line 27, has been amended as follows:

For example, CLASP-2A and CLASP-2C are related to each other as apparent splice variants, with CLASP-2C containing an exon not found in CLASP-2A. The exon sequence is 5'-AGG GAT TTT GAG AGG CTG GCC CAT CTG TAT GAC ACG CTG CAC CGG GCC TAC AGC AAA GTG ACC GAG GTC ATG CAC TCG GGC CGC AGT TNC TGG GGA CCT ACT TCC GGG TAG CCT TCT TCG GGC AG-3' (SEQ ID NO:93) (encoding the peptide sequence:

RDFERLAHLYDTLHRAYSKVTEVMHSGRRLLGTYFRVAFFGQGF (SEQ ID NO:94)).

It will be apparent to one of skill that, by using polynucleotide probes or primers corresponding to the nucleic acid sequence above, or by using antibodies that specifically recognize the peptide above, or those polynucleotide probes or primers shown in Table 3 below, it is possible to distinguish between different CLASP isoforms(*e.g.*, to detect differential expression).

Table 3 on page 39 has been amended as follows:

Table 3

	Found in/will detect	Exemplary Probe/Primer (5' – 3')	<u>SEQ ID NO</u>	Notes/Comments
1	full length hC2A	F1: CCCAGATTTTATGATGAG R1: GATAATGACAAAGTTCTGAC	<u>95</u> <u>96</u>	
2	full length hC2D	F2: CTGGAAATCTTGACAAAAATGC R2: GTCTTTTAAATACAGATGTGG	<u>97</u> <u>98</u>	
3	hC2B, hC2C, hC2E	F3: GAGAGGCTGGCCCATCTGTATG R3: ATCTTCAAAGAATCCCTGCC	<u>99</u> <u>100</u>	Distinction based upon product size differences following PCR
4	hC2D	F4: GAAGCAGTCCAGTGGGAGCCG R4: GCCTCCCCGGCTCCTCCTCAGG	<u>101</u> <u>102</u>	Recognizes hC2D-specific insertion
5	hC2D	F3: GAGAGGCTGGCCCATCTGTATG R5: CCTCCACATCTGTTTCACTGTC	<u>99</u> <u>103</u>	
6	hC2E	F5: CTCCATGATGGAAGACGTGGG R6: GATGAGCTCGTAGCGCTCGGC	<u>104</u> <u>105</u>	Spans deletion unique to hC2E. Distinction based upon product size differences following PCR
7	hC2B	F6: CATTGGCGTTTAAGCTCCTG R3: ATCTTCAAAGAATCCCTGCC	<u>106</u> <u>100</u>	F6 primer spans deletion unique to hC2E
8	hC2A	F7: GGACCCATAGTTCATGATCG R4: CTTTCATCTTCAAGAAATCCCTC	<u>107</u> <u>108</u>	R4 primer spans the region where other CLASPs have an insert

The paragraph beginning on page 42, line 20, has been amended as follows:

Exemplary CLASP-2 polynucleotide fragments are preferably at least about 15 nucleotides, and more preferably at least about 20 nucleotides, still more preferably at least about 30 nucleotides, and even more preferably, at least about 40 nucleotides in length, or larger 50, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650 nucleotides. In one embodiment, exemplary fragments include fragments having at least a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600 to the end of SEQ ID NO:1 or SEQ ID NO:[____] 3 or comprising the cDNA coding sequence in the deposited clones. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

The paragraph beginning on page 43, line 20, has been amended as follows:

In one embodiment, the CLASP-2 variants differ from those shown in FIG. 1 or FIG. 11 (SEQ ID NO[s] 1, 2, [3, 5, 7, 9, _____] 115, 116, 117, 118, and 119) by virtue of incorporating a different combination of exons than found in the exemplified sequences. For example, 81g01 (Genbank Accession Number AF85864; Locus HUMYN81g01; 526 bp; EST sequence submitted August 29, 1998 by Washington University at St. Louis; see FIG. 3A and FIG. 3B) is a variant of hCLASP-2 on the basis of CLASP-2 identity along certain stretches of the sequence. From 5' to 3', it begins with a 315 nucleotide stretch which is identical to CLASP-2A. It then has a gap relative to CLASP-2A that is identical to the GAP in another CLASP-2 isoform, hCLASP-2D (KIAA1058). In place of that gap, a 16 amino acid insert (48 nucleotides) is present which is not found in other isoforms, followed by another approximately 150 bp stretch of nucleotides once again identical to CLASP-2A. This is characteristic of an alternate splice due to the specific sequence identity on both sides of a differential stretch of nucleotides.

The paragraph beginning on page 45, line 3, has been amended as follows:

In various embodiments, CLASP-2 polynucleotide fragments include coding regions for, or regions hybridizable to, the CLASP-2 structural or functional domains described *supra*. As set out in the Figures, such preferred regions include the following domains/motifs: ITAM, DOCK, COILED/COILED, and PBM. Thus, for example, polypeptide fragments of CLASP-2 as shown in FIG. 1 and FIG. 11-(SEQ ID NO:[2, 4, 6 10, _____] 1, 2, 115, 116, 117, 118, and 119) falling within conserved domains are specifically contemplated by the present invention (see FIG. 3). Moreover, polynucleotide fragments encoding these domains are also contemplated. Such polypeptide fragments find use, for example, as inhibitors of CLASP-2 function in CLASP-2-expressing cells.

The paragraph beginning on page 57, line 13, has been amended as follows:

In one embodiment, the antisense sequence is complementary to relatively accessible sequences of the CLASP-2 mRNA (*e.g.*, relatively devoid of secondary structure). This can be determined by analyzing predicted RNA secondary structures using, for example, the MFOLD program (Genetics Computer Group, Madison WI) and testing in vitro or in vivo as is known in the art. Another useful method for identifying effective antisense compositions uses combinatorial arrays of oligonucleotides (see, *e.g.*, Milner *et al.*, 1997, Nature Biotechnology 15: 537). Examples of oligonucleotides that can be tested in cells for antisense suppression of CLASP-2 function are those capable of hybridizing to (*i.e.*, substantially complementary to) the following positions from SEQ[UENCE] ID NO:1:

- 1) GAAGGCGATCATCACGTGGCCTTCCATCGC
(SEQ ID NO:109)
- 2) GCTTCAAGTAATGACTGGTGCAGAACATCTG
(SEQ ID NO:110)
- 3) GCTCCTCCTCAGGCAGGCGCTATGGCTGTGG
(SEQ ID NO:111)
- 4) GTAGGCCCGGTGCAGCGTGTACATACAGATGG
(SEQ ID NO:112)

(See also Example [8] 7B, Table 5)

The paragraph beginning on page 58, line 4, has been amended as follows:

The antisense nucleic acids (DNA, RNA, modified, analogues, and the like) can be made using any suitable method for producing a nucleic acid, such as the chemical synthesis and recombinant methods disclosed herein. In one embodiment, for example, antisense RNA molecules of the invention can be prepared by *de novo* chemical synthesis or by cloning. For example, an antisense RNA that hybridizes to CLASP-2 mRNA can be made by inserting (ligating) an CLASP-2 DNA sequence (*e.g.*, SEQ[UENCE] ID No:1, or fragment thereof) in reverse orientation operably linked to a promoter in a vector (*e.g.*, plasmid). Provided that the promoter and, preferably termination and polyadenylation signals, are properly positioned, the strand of the inserted sequence corresponding to the noncoding strand will be transcribed and act as an antisense oligonucleotide of the invention. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter or enhancer) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

Please replace the paragraph beginning on page 109, line 6, with the following amended paragraph:

The following cDNA clones described in the Specification and further described in the Examples below have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209 under the Budapest Treaty on [] October 17, 2000 and given the Accession Nos. indicated:

hCLASP-2 clone hC2GR3.3 (AVC-PD14) ATCC Accession No.

[] PTA-2611

hCLASP-2 clone hC2RT (AVC-PD19) ATCC Accession No. []

PTA-2614

The Primer Table, on page 112, has been amended as follows:

Primer Table

CLASP gene	Sense Primer	Sense sequence (SEQ ID NO:)	Antisense Primer	Antisense sequence
CLASP-7	HC7gS5	AGGCCTTGTCTCTGTTTACCTG SEQ ID NO:140	HC7gAS1	TGTCATGTACTGCACTCGCACAGC SEQ ID NO:146
CLASP-7	HC7gS3	ACAGGAACCTGCTGTACGTGTAC SEQ ID NO:141	HC7AS14	TCGTGGCTGCACAGGATGCGGGTG SEQ ID NO:147
CLASP-4	C4P2	GACCCATTAGGAGGTCTAC SEQ ID NO:142	HC4AS3'	CGGGATCCATTGTCACCGTACATCT GC SEQ ID NO:148
CLASP-4	C4P2	GACCCATTAGGAGGTCTAC SEQ ID NO:143	HC4AS3'	CGGGATCCATTGTCACCGTACATCT GC SEQ ID NO:149
CLASP-1	hC1S5'	TATGTCTCAGTCACCTACCTG SEQ ID NO:144	HC1AS3'Kpn	CTTGGTACCACTTCAGCACTAGATG AGATG SEQ ID NO:150
CLASP-1	C1S7	TCAAGACCAGGGCATGCAAG SEQ ID NO:145	HC1AS3'Kpn	CTTGGTACCACTTCAGCACTAGATG AGATG SEQ ID NO:151

The paragraph beginning on page 112, line 7, has been deleted and replaced with the following table:

Primer	Sequence (5' to 3')	SEQ ID NO:	Nucleotide Position
HC2RACE1	AAGAGCAGCATCTCCCGTAAACAGTC	152	-15 to 11
HC2RACE2	TAACAAGCTCTGTGCTTCCTCTTCCG	153	414 to 443
HC2RACE3	ACCACTTTGTTGGAAGCTGTGAAACT C	154	512 to 540
HC2RACE4	TTTGTACAGCCAGCCATGCTTGGTGATC	155	634 to 661

Table 5, on page 119, has been amended as follows:

Table 5

Oligo	Sequence 5'-3' (SEQ ID NO:)	length	notes/comments
1	GAAGGCGATCATCACGT GGCCTTCCATCGC (SEQ ID NO:109)	30-mer	encompasses nucleotides 473-502 and spans the putative initiator methionine (underlined). The function of HC2A, 2B, 2C, and 2E isoforms can be eliminated by this oligonucleotide.
2	GCTTCAAGTAATGACTGG TGCAGAACATCTG (SEQ ID NO:110)	31-mer	Oligonucleotide that should recognize HC2A, 2B, 2D, 2E, and 2F. Encompasses nucleotides 2121-2151. Can be eliminate function of these CLASP-2 isoforms.
3	GCTCCTCCTCAGGCAGGC	34-mer	oligonucleotide specific for HC2C based upon a

	GCTATGGCTGTGG (SEQ ID NO:111)		specific exon found at nucleotide 2927. Can eliminate only HC2D function.
4	GTAGGCCCGGTGCAGCGT GTCATACAGATGG (SEQ ID NO:112)	31-mer	oligonucleotide specific for HC2B, 2C, 2D and 2E based upon specific exon sequence found at nucleotide 3153. Can eliminate function of these CLASP-2 isoforms.
5	GCAATGTCTGAGACTTTC GATCATGAACTATG (SEQ ID NO:113)	32-mer	oligonucleotide specific for HC2A, 2B, 2E, and 2F. Encompasses nucleotides 1987-2018. Can eliminate function of these CLASP-2 isoforms.
6	CAGGAGCTGGTTCTTAAA (SEQ ID NO:114)	18-mer	oligonucleotide specific for HC2A, 2D and 2E. Encompasses nucleotides [2219-2224] 2213-2230. Can eliminate function of these CLASP-2 isoforms

Table 5 legend. All nucleotide numeration are relative to Human CLASP-2A (HC2A). See FIG. [2A] 2B.